Case report

Adult-onset methylenetetrahydrofolate reductase deficiency

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SUMMARY

Severe hyperhomocysteinemia (>100 µmol/L) is often associated with inborn errors of homocysteine metabolism. It manifests typically in neonatal period with developmental delay, hypotonia, feeding problems or failure to thrive. Adult-onset forms are rare and include less severe manifestations. Early diagnosis is crucial because effective treatment is available. A 23-year-old man presented with a 3-week history of speech and gait impairment, and numbness in lower limbs. Neurological examination revealed dysarthria, decreased vibratory sensation in both legs and appendicular and gait ataxia. Brain MRI revealed T2-hyperintense symmetric white matter lesions and cortical atrophy. He had folate and vitamin B_{12} deficiency, a markedly elevated serum homocysteine and low methionine. Despite vitamin supplementation homocysteine levels remained elevated. Molecular studies of 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene revealed a new pathogenic mutation (c.1003C>T (p.Arg335Cys)) and a polymorphism (C677T (p.Ala222Val)) associated with hyperhomocysteinemia, both in homozygosity. The patient started betaine with clinical and biochemical improvement.

BACKGROUND

Methylenetetrahydrofolate reductase (MTHFR) is a cytoplasmic enzyme that catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Mutations in *MTHFR* gene lead to hyperhomocysteinemia and homocystinuria due to abnormalities in the remethylation of homocysteine (Hcy) to methionine. Even mild hyperhomocysteinemia represents an important risk factor for atherosclerosis and vascular disease, including stroke, and it also contributes to the development of cognitive impairment.[1]

Severe MTHFR deficiency leading to severe hyperhomocysteinemia is a rare disorder, and its prevalence is unknown. Patients typically present in neonatal period with feeding problems, failure to thrive, muscular hypotonia, encephalopathy or seizures.[2] Vascular pathology is less frequent. Late-onset disease (>1-year old) occurs less frequently and with more variable manifestations including neurocognitive impairment, gait abnormalities, neurological disturbance compatible with myelopathy or ataxia, psychiatric disorders or thromboembolic events.[2] If untreated, patients with severe MTHFR deficiency may exhibit significant developmental delay, mental retardation and, in some cases, epilepsy and severe neurological impairment, which leads to the need of long-term care.[2] Brain atrophy and white matter disease are present in most patients.[3] Early treatment with betaine prevents cognitive damage and reduces mortality.[4] Froese *et al* summarised, in 2016, the variants reported in the literature in families with severe MTHFR deficiency. There were 192 patients from 171 families, with a total of 109 mutations described. Only 121 patients had a defined time of clinical presentation, of which 56 had a late-onset presentation.[3] An additional pathogenic mutation was described recently in a patient with compound heterozygosity.[5]

This case is about a late-onset hyperhomocysteinemia due to MTHFR deficiency associated with a novel pathogenic mutation (c.1003C>T (p.Arg335Cys)) and a polymorphism (C677T (p.Ala222Val)), both in homozygosity.

CASE PRESENTATION

A 23-year-old man presented with a 3-week history of insidious dysarthria, gait impairment and numbness in both legs. He reported no weakness, headache, visual symptoms or any other problems. He denied recent infection or trauma. His medical history was unremarkable, including a full-term pregnancy and a normal psychomotor development. His parents were half-siblings; there was no history of hereditary diseases. He had a diversified diet, had no smoking or alcoholic habits, or history of illicit drug consumption. Neurological examination revealed dysarthria, a saccadic ocular pursuit, global hyperreflexia, a markedly reduced vibratory sensation on both lower limbs with a positive Romberg test, an intentional symmetric upper limb tremor, gait ataxia, and bilateral *pes cavus*.

INVESTIGATIONS

Serum vitamin investigations revealed decreased vitamin B_{12} (97 pg/mL; range value (RV): 175–1500 pg/mL) and folate (1.4 ng/mL; RV: 3–20 ng/mL). Blood count, biochemical analysis and serologic studies were normal. Autoimmunity study, including for pernicious anaemia and coeliac disease, was negative. Brain MRI showed T2-hyperintense lesions without contrast enhancement on both *corona radiata*, bilateral semioval centres, periventricular and on right cerebellar hemisphere, and a global cortical atrophy (figures 1 and 2). Lower limb somatosensitive potentials revealed a bilateral increased latency. The electromyogram and upper digestive endoscopy were normal.

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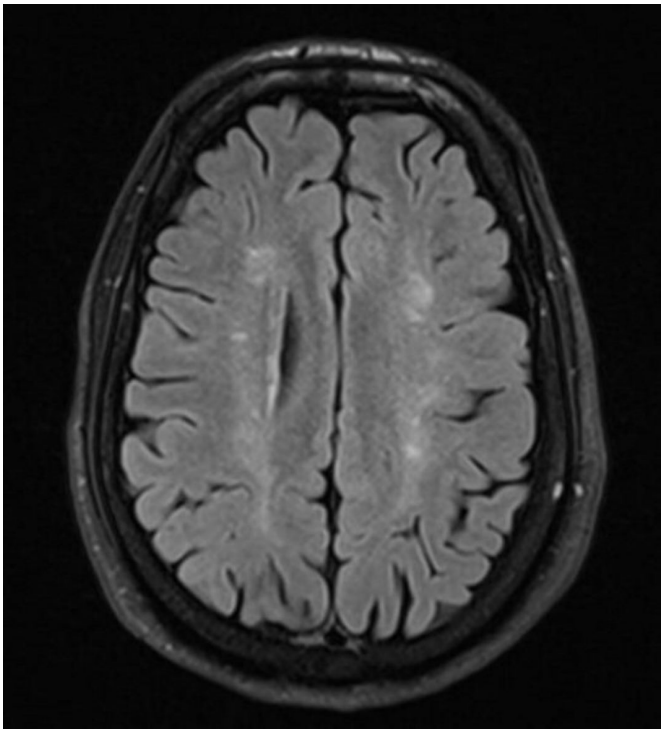

Figure 1 Brain MRI images showing T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) hyperintense lesions without gadolinium enhancement on both *corona radiata*/semioval centres bilaterally.

Patient initiated vitamin B_{12} and folate supplementation leading to a normalisation of its serum levels but without any clinical improvement. Patient reported asthenia and subjective memory problems, and he had increasing difficulties at work; despite that, neurological examination remained stable.

Further diagnostic workup revealed increased levels of Hcy, both on plasma (202 µmol/L; RV: 5 –15 µmol/L) and urine (18.9

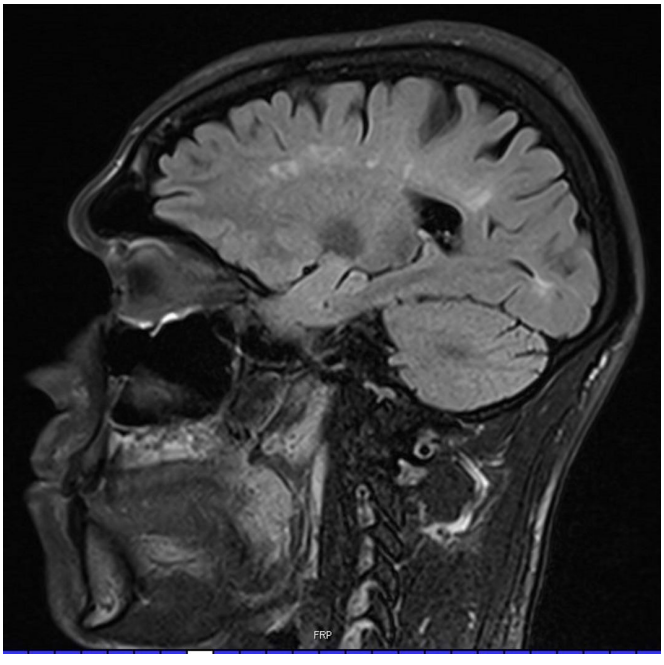

Figure 2 Brain MRI images showing T2-Fluid-Attenuated Inversion Recovery (FLAIR) hyperintense lesions without gadolinium enhancement on *corona radiata*/ semioval centresand cortical atrophy.

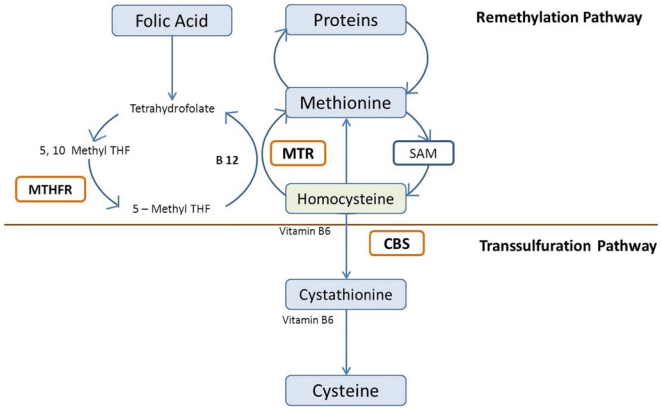

Figure 3 Homocysteine metabolism pathways. CBS, cystathionine β-synthase; MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase; SAM, S-adenosylmethionine (adapted from Kadhim and Clement [7]).

µmol/mmol creatinine (Cr); RV: 0.20–4 µmol/mmol Cr), even after correction of vitamin B_{12} and folate deficiency.

Plasma amino acid profile was normal including a normal level of methionine (40.7 µM; RV: 8.7−40.9 µM); urinary amino acid profile had no abnormalities except for a slight decreased level of methionine (1.4 µmol/mmol Cr; RV: 2.0–16.0 µmol/mmol Cr). The urinary organic acids showed no abnormalities including a vestigial methylmalonic acid. Study of *MTHFR* gene revealed the pathogenic mutation c.1003C>T (p.Arg335Cys) in homozygosity, in exon 5, confirming the diagnosis of MTHFR deficiency since p.Arg335Cys is associated with homocystinuria. Additionally, it was detected the polymorphism C677T (p.Ala222Val) in homozygosity in exon 5.

DIFFERENTIAL DIAGNOSIS

Hcy is involved in two metabolic pathways—the remethylation pathway, in which MTHFR and methionine synthase (MTR) leads to methionine synthesis; and the transsulfuration pathway, where cystathionine β-synthase degrades Hcy to cysteine (figure 3).

Severe hyperhomocysteinemia (>100 µmol/L) is essentially pathognomonic for the presence of an inborn error of Hcy metabolism causing homocystinuria.[6 7] This patient has a severe hyperhomocysteinemia *ab initium* which raised the suspicion of a genetic defect. He had vitamin B_{12} deficiency too and, despite vitamin supplementation, plasma Hcy remained elevated, which raised the possibility that another mechanism was contributing to hyperhomocysteinemia. The patient had no other identifiable causes of elevated Hcy.

Within the group of genetic homocystinurias, plasma metabolite profile and urinary methylmalonic acid can be helpful in the diagnosis of MTHFR deficiency. Differential diagnosis is summarised in table 1.

Table 1 Causes of severe hyperhomocysteinemia and serum abnormalities

Disease	Enzyme/cofactor	Hcy	Met	MMA
Classical homocystinuria	Cystathionine β-synthase	↑	↑	N
Cobalamin deficiency	Cobalamin	↑	↓	↑
MTHFR deficiency	MTHFR	↑	N/↓	N

Hcy, homocysteine; Met, methionine; MMA, methylmalonic acid; MTHFR, methilenetetrahydrofolate reductase.

TREATMENT

After normalisation of vitamin B_{12} and folic acid, blood levels achieved with appropriated supplementation, the patient began specific treatment with betaine, a methyl group donor, 3 g three times a day, with clinical improvement.

OUTCOME AND FOLLOW-UP

Patient maintains treatment with betaine and vitamin supplementation and after 3 years of follow-up he keeps clinical improvement. He reports stabilisation of memory problems, which do not interfere with daily activities. On neurological examination, he maintains global hyperreflexia and a reduced vibratory sensation on both lower limbs, but there is a significant improvement of limb ataxia and gait unsteadiness. Serum Hcy decreased, but remains elevated (100 µmol/L) despite the treatment. Brain MRI abnormalities remain stable, without new white matter lesions or atrophy worsening.

DISCUSSION

This case illustrates a late presentation of a rare inborn error in Hcy metabolism. It is inherited in an autosomal recessive manner and typically presents in neonatal period.[2] In a study with 30 patients, median age at onset of symptoms was 1.25 months (range 0.1 months to 18 years).[2] Consanguinity was present in 13 families. The main presenting clinical symptoms were muscular hypotonia, feeding problems, failure to thrive, developmental delay/mental retardation, microcephaly and signs of encephalopathy. In severe MTHFR deficiency, adolescents and adults may present with psychiatric symptoms, neuropathy or thromboembolic events.[8] Lossos *et al* also reported two unrelated families, each with two siblings with severe MTHFR deficiency manifesting a spastic paraparesis, polyneuropathy, behavioural changes, cognitive impairment, psychosis, seizures and leukoencephalopathy starting between the ages of 29 and 50 years.[9] Treatment with betaine produced a rapid decline in Hcy in all patients and improved symptomatology in three patients. Bathgate *et al* also described two young-adult siblings with a spastic paraparesis who developed cognitive decline and behavioural disturbance, in relation with a severe hyperhomocysteinemia.[10]

In this late-onset clinical case, the main manifestations were neurological, including severe ataxia, impaired vibratory sensation and leukoencephalopathy. The predominance of white matter disease and brain atrophy is caused by a defective myelination due to cerebral deficiency of S-adenosylmethionine, which may be reversed with treatment.[9 11]

Individuals who carry the polymorphous C677T in homozygosity tend to have higher Hcy levels and lower serum folate levels compared with controls.[12] Also, according to Kirke *et al*, MTHFR polymorphism in heterozygosity, which is present in 38% of the population, increases the risk of neural tube defects.[13]

The pathogenic mutation p.Arg335Cys in *MTHFR* gene was described once by Goyette *et al* in 1995 and is associated with hyperhomocystinuria.[14] There are no reported cases in the literature with the mutation c.1003C>T (p.Arg335Cys).

Since causal treatment for MTHFR deficiency is not available, betaine is the mainstay of symptomatic treatment.[3] Biochemical improvement is frequently associated with symptomatic recovery, suggesting the importance of early treatment to prevent irreversible deterioration.[9] Therefore, this diagnosis may be kept in mind in patients with a compatible history. Tests for plasma Hcy and serum amino acids levels would be expected to show an elevated Hcy and low methionine. *MTHFR* full sequencing can confirm the suspected clinical diagnosis.[15]

Learning points

- Inborn errors of metabolism may have a late-onset presentation.
- Severe hyperhomocysteinemia may have neurological and psychiatric manifestations and is mostly associated with genetic abnormalities.
- Patient prognosis depends on early diagnosis and specific treatment.

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